130. The method of claim 98, wherein said subject is a human.

131. The method of claim 98, wherein said immune effector cell is a CTL.

132. The method of claim 98, wherein step (iv) further comprises administering to said subject at least a first cytokine.

133. The method of claim 132, further comprising administering to said subject a second cytokine, different from said first cytokine.

134. The method of claim 132, wherein said cytokine is selected from the group consisting of GM-CSF, IL-4, C-KIT, Steel factor, TGF-β, TNF-α and FLT3 ligand.

135. The method of claim 132, wherein said cytokine is administered as a gene encoded by said expression construct.--

III. REQUEST FOR RECONSIDERATION

A. Status of the Claims

Claims 1-37 were pending at the time of the Action and stand rejected, variously, under 35 U.S.C. §112, first paragraph, 35 U.S.C. §102 and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below. Claim 32 has been canceled herein as duplicative in view of the amendment to claim 1. Claims 38-60 have been canceled without prejudice as drawn to non-elected subject matter. Applicants reserve the right to file continuing applications directed to this subject matter. New claims 61-135 have been added herein. Claims 1-31, 33-37 and 61-135 are now pending in the case and presented for reconsideration. Support for the new claims may be found in the specification as originally filed in the case. In particular, support can be found as follows:

Support for claim 61 can be found, at least, from page 8 , line 25 to page 9, line 2; from page 60, line 8 to page 61, line 26; at page 71, lines 13-26 and from page 72, lines 26-29.

Support for claims 62-71 can be found, at least, from page 6, line 23 to page 7, line 12.

Support for claims 72-82 can be found, at least, at page 7, lines 13-28.

Support for claims 83-85 can be found, at least, at page 8, lines 1-7.

Support for claims 86-90 can be found, at least, at page 8, lines 18-23.

Support for claim 91 can be found, at least, at page 65, lines 3-10.

Support for claims 92-97 can be found, at least, at page 8, lines 9-15.

Support for claims 98-99 can be found, at least, from page 8 , line 25 to page 9, line 2; from page 60, line 8 to page61, line 26; at page 71, lines 13-26 and from page 72, lines 26-29.

Support for claims 100-109 can be found, at least, from page 6, line 23 to page 7, line 12.

Support for claims 110-120 can be found, at least, at page 7, lines13-28.

Support for claims 121-123 can be found, at least, at page 8, lines 1-7.

Support for claims 124-128 can be found, at least, at page 8, lines 18-23.

Support for claim 129 can be found, at least, at page 65, lines 3-10.

Support for claims 130-135 can be found, at least, at page 8, lines 9-15.

B. Rejections Under 35 U.S.C. §112, First Paragraph

The Action rejects claims 1-4 and 11-37 under 35 U.S.C. §112, first paragraph as allegedly not being enabled by the specification. Applicants respectfully traverse as set forth below.

1. The Action Misapplies The Legal Standard for Enablement

Applicants first note that a common thread running through many of the rejections in the Action is that Applicants' claims are said to lack enablement for each and every embodiment that might be covered. For example, the Action states that the specification "does not reasonably provide enablement for treating *any* type of hyperproliferative disease comprising the intradermal administration of *any* type of expression construct encoding *any* tumor supressor gene."

Emphasis added, Action at page 2. It thus appears that the Action misapplies 35 U.S.C. §112, first paragraph, and what is required for its satisfaction. Therefore, before proceeding with a discussion of the facts at issue here, Applicants wish to clarify this point of law.

It is settled that enablement must bear only a *reasonable* relationship to the scope of the claims. *In re Fisher*, 166 U.S.P.Q. 18, 24 (CCPA 1970). It has also been established that it is not the function of the claims to exclude potentially inoperable species. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409 (Fed. Cir. 1984). Moreover, the Federal Circuit has stated that "[t]he enablement requirement is met if the description enables ***any*** mode of making and using the invention." *Johns Hopkins Univ. v. CellPro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998) (emphasis added) (quoting *Engel Indus. Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991)). Further, "[a] patent applicant is not required . . . to predict every possible variation, improvement or commercial embodiment of his invention." *United States Steel Corp. v. Phillips Petroleum Co.*, 673 F. Supp. 1278, 1292 (D. Del. 1987), *aff'd*, 865 F.2d 1247, 1250 (Fed. Cir. 1989) (specifically quoting this statement). This is echoed in the MPEP: "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970)). Thus the applicable legal standard does *not* require that all conceivable embodiments encompassed by the claims have been demonstrated to be operable. Rather, the claims must only bear a reasonable relationship to the enabled subject matter. Applying this correct standard, as explained below, the present claims are fully enabled.

2. The Specification Enables the Treatment Of Cancer

The Action alleges that the specification does not provide an enabling disclosure for the treatment of "any cancer comprising the intradermal administration of any tumor suppressor gene." The basis of the rejection is that each cancer arises from multiple and different mutations and that different types of cancer may have different mutations. It is thus stated that successful use of the invention would require detailed knowledge of the genetic mutations of a particular type of tumor to ensure that an immune response would recognize the target tumor cell. In making the rejection, the Action quotes extensively from Vogelstein *et al.* (*Trends in Genetics*, 9(4):141, 1993). The main points derived from this article are (a) that each tumor may have different sets of mutations; (b) that most mutations are in either tumor suppressors or oncogenes; and (c) that tumors may acquire new mutations over time. Each of these statements appears to be true. However, individually or taken together, they bear very little on the enablement of the present invention.

First, while it is true that tumors may have different sets of mutations, it is well known that p53 is perhaps the most common site of mutation in cancers, with roughly 50% of all tumors showing such defects. This is indicated in the Action itself, on page 10, which cites Hurpin *et al.*, ((1998) Vaccine, Vol. 16, No. 2/3, 208-215) for the proposition that "***more than 50% of tumors overexpress p53***." (emphasis added). Further, the working examples in the specification demonstrate the enablement for p53. For instance, Example 4 in the specification describes studies showing that immunization of mice with Ad-p53 dendritic cells results in CTL responses against mutant murine p53. Further, Example 5 shows that CTL and T-cell induced immune responses provide tumor protection in mice. For example, in mice immunized with Ad-p53 DC, 17 out 20 (85%) were completely protected against D459 tumor cells and 8 out 11 mice (72.7%)

were protected against MethA sarcoma. Further, in a study of the effect of treatment of established poorly immunogeneic tumors with repeated injections with Ad-p53 infected dendritic cells, it was shown that treatment of mice with Ad-p53 infected DC significantly slowed tumor growth. See FIG. 4 of specification.

3. The Specification Enables Treatment of Hyperproliferative Diseases by Intradermal Injection

The Action alleges that, although the specification provides working examples of intravenous, subcutaneous and intraperitoneal injection with adenovirus p53, the disclosure is not enabling for treatment of hyperproliferative diseases by intradermal injection. However, no scientific evidence for doubting the enablement of intradermal administration of expression constructs is provided in the Action. Further, Applicants note that recent studies have demonstrated the efficacy of intradermal administration of adenoviral vectors to elicit potent humoral and cellular immunity. For example, Gilbert *et al.* (*Vaccine* 15;20(7-8):1039-45, 2002) found that recombinant replication-defective adenovirus expressing the CS gene from *Plasmodium berghei* (Ad-PbCS) induced a strong CD8(+) T cell response after intra-dermal or -muscular injection. Potent immune responses for intradermal administration of Adenovirus were also found, for example, by Anand *et al.* (*Mol Ther* 5(2):125-32, 2002). Finally, Harvey *et al.* (Hum Gene Ther., 20;10(17):2823-37, 1999), demonstrated that intradermal administration of adenoviral effectors to humans elicits local immune responses and is safe, even in Ad-immunized individuals. Therefore, in view of the working examples in the specification using intravenous, subcutaneous or intraperitoneal injection; the lack of any scientific reason for doubting the enablement of the claimed invention and the evidence provided, Applicants have more than

adequately demonstrated the enablement of intradermal administration in connection with the invention.

With respect to hyperproliferative diseases in general, it is noted that these conditions are typified by dysregulated growth, without neoplastic transformation. A number of recent independent studies have shown that the genes underlying cellular growth control, for example, tumor suppressor genes and oncogenes, can be mutated and/or expressed aberrantly in hyperplastic conditions which either do not or only rarely progress to cancer. For example, p53 has recently been implicated as having a role in rheumatid arthritis. *See, e.g., Yamanishi et al., Rheum Dis Clin North Am.*, 27(2):355-71, 2001; *see also* Muller-Ladner *et al., Arthritis Res.* 2(3):175-8, 2000. Mutations in p53 have also now been found in additional hyperproliferative conditions, such as lichen sclerosus. *See, e.g.,* Carlson *et al., Appl. Immunohistochem. Mol. Morphol.*, 9(2):150-63, 2001. These common mechanisms indicate the broad applicability of the invention

4. The Specification Enables Therapeutic Expression of Vectors

The Action alleges generally that achieving therapeutic levels of expression using currently available vectors is unpredictable. In particular, the Action cites various articles said to challenge generally the ability to achieve gene expression. However, the Action has not offered any reasoning why, once the general principle of adenoviral p53 has been established, those of skill in the art could not reproduce the work using other vectors, for example, adenovirus strains. The standard of enablement involves a person of ordinary skill in the art, who has knowledge of the art. No evidence has been provided to indicate that that person would not be able to employ the teachings of the application with his or her knowledge of the art and construct additional p53

adenoviral vectors. Examples need not be presented for every single embodiment of this aspect of the invention. *In re Borkowski*, 164 U.S.P.Q. 624 (CCPA 1970).

An assertion that the disclosure is not commensurate with the scope of the claims must be supported by evidence or reasoning substantiating the doubts advanced. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (CCPA 1974). The Action has attempted to achieve this by the citation of numerous articles. As explained below, these citations fall short of what is needed to support the rejection.

For example, the Action relies on three references in arguing against the predictability of generating therapeutic levels of gene expression. However, it must be understood that unpredictability is not grounds for non-enablement, it is merely a factor. Moreover, the particular portions of these papers relied upon by the Action evince other misconceptions about the requirements of §112, first paragraph. For example, Verma *et al.* is said to report that "[t]he Achilles heel of gene therapy is gene delivery" and that "most of the approaches suffer from poor efficiency of delivery and transient expression." However, all that is required for enablement is *objective* enablement, not any particular level of efficacy. *In re Marzocchi*, 169 UPSQ 370 (CCPA 1971). One must wonder how the PTO has issued dozens of patents on gene therapy and on gene delivery systems if the underlying premise of gene delivery and expression is flawed. Even were one to answer that "each case is decided on its own merits" - such a comment does not address the issue at bar. The Action's reliance on the Verma article clearly relates to doubting that current vector systems *are capable of expressing therapeutic proteins in vivo*. However, the number of issued patents that bear on *this issue* indicates otherwise.

In the Action, Marshall *et al.* (1995) is quoted as stating that "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-- remain a nagging problem for the field" and that "many problems must be solved before gene therapy will be useful for more

than the rare application." However, both of these statements indicate that, while potentially hampered by limitations, gene therapy does in fact work. This parallels the quotes from Orkin *et al.* (1995) which only state that "none of the available vectors systems are ***entirely*** satisfactory, and many ... have not been experimentally ***validated.***" Emphasis added. Again, this speaks to optimization, not bare operability. This is irrelevant, as enablement is not judged based on commercial applicability or optimization. Finally, Orkin states that "clinical efficacy has not been definitively demonstrated at this time ...." However, neither the demonstration of clinical effectiveness or an approval of a product by the Federal Drug Administration (FDA) is required to enable the instant invention – the PTO is not the FDA.[1] Thus, despite the Action's attempt to "support" the rejection with these citations, it is respectfully submitted that such "evidence" and "reasoning" falls far short of that needed to establish a *prima facie* case of lack of enablement.

In conclusion, the Action has failed to demonstrate the lack of enablement of the claims. Removal of the rejection is thus respectfully requested.

C. Rejections Under 35 U.S.C. §102

The Action rejects claims 1-4, 11, 20-30 and 33 under 35 U.S.C. §102(b) as allegedly anticipated by Hurpin *et al.* (Vaccine, Vol. 16, No. 2/3, 208-215 (1998)). Applicants respectfully traverse.

Hurpin *et al.* (1998) is directed to various expression constructs used in various routes of administration for expression of wild-type p53 and generating a specific CTL response thereto.

[1] See also *In re Krimmel*, 130 U.S.P.Q. 215, 219 (CCPA 1961) ("We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.")

Hurpin *et al.* refers to measurement of CTL responses by assaying lysis of splenocytes, and also through protection against challenge following immunization with wild-type p53 gene. However, unlike the current claims, the Hurpin reference teaches these approaches in model ***mice***, not humans. Thus, the issue over novelty is moot. Further, there is no specific mention of expression of the self gene product, here p53, by dendritic cells or the presentation of the antigen to immune effector cells. Furthermore, Hurpin teaches that intradermal injection of canarypox virus does ***not*** work, whereas intradermal injection of naked DNA ***does***. Thus, one skilled in the art would not expect success generally, much less success using another virus like adenovirus.

In contrast to Hurpin *et al.*, the current claims involve *human* treatment regarding delivery of an expression construct comprising the self-gene product *in vivo* or *ex vivo* into the dendritic cell to elicit anti-tumor immune responses. The current claims further specify that the expression construct is delivered in a viral particle. In contrast, the canarypox data of Hurpin *et al.* teaches away from the use of intradermal administration of viral particles, given that intravenous administration was the only route that worked for canarypox-p53. In contrast to Hurpin's intradermal administration of naked DNA eliciting tumor responses, Applicants here teach that the gene delivery vehicle is advantageously introduced into dendritic cells by way of the viral particle, preferably *in vivo*, for anti-tumor responses. Thus, the presently pending broad claims of the application are not affected by the limited teachings of the Hurpin *et al.* reference. Therefore, Hurpin *et al.* fails to be novelty-defeating for all elements of the claims. Removal of the rejection under 35 U.S.C. §102 is thus respectfully requested.

D. Rejection Under 35 U.S.C. §103

1. *Rejection of claims 1, 12-19 and 32 under 35 U.S.C. §103(a) over Hurpin et al. in view of Fang et al. and Reed et al.*

The Action rejects claims 1, 12-19 and 32 under 35 U.S.C. §103(a) over Hurpin *et al.* in view of Fang *et al.* (U.S. Patent No. 6,110,744) and Reed *et al.* ((1997) Int. J. Cancer, Vol. 72, 1045-1055). Applicants respectfully traverse.

Hurpin *et al.* (1998) teaches away from the present invention and thus is not properly combinable with Fang *et al.* or Reed *et al.* In particular, Hurpin teaches that intradermal injection of canarypox virus does *not* work, whereas intradermal injection of naked DNA *does*. For example, the Abstract of Hurpin states that "For the [recombinant canarypox virus], intravenous but not subcutaneous, intramuscular or intradermal administration, induced CD8+ CTLs that lysed tumor cells transfected with human mutant p53." Further, Hurpin *et al.* states on page 210, in the second full paragraph of column 2, that intradermal administration of vector vCP207, a recombinant canarypox vector expressing p53, "failed to elicit any specific anti-p53 CTLs [*figure 1(A)*] and addition of GM-CSF in the form of recombinant protein (500 or 5000 units) or vCP319 had no effect (data not shown)." Even using the indicated "optimal" mode of intravenous administration, a study of protection from tumor challenge with the canarypox vector yielded only "..partial, but not statistically non-significant (P> 0.25 vs. PBS) protection with only one out of nine mice remaining tumor-free by week 15." Hurpin *et al.*, second paragraph, page 212. Still further, Hurpin *et al.* indicates that administration of the ALVAC vector itself was not only not protective, but rather appeared to slightly accelerate tumor growth relative to PBS. See Hurpin *et al.*, second paragraph, page 212.

The second paragraph of page 212 of Hurpin *et al.* also indicates that complete protection was obtained by the administration of naked pC53-SN_3 plasmid DNA. Therefore, if anything, Hurpin *et al.* teaches the use of naked DNA and *teaches away from use of viral particles as required by claim 1*. Even if Hurpin *et al.* is alleged to teach delivery of expression constructs with viral particles, it *teaches away from the intradermal administration of any such viral particles*. That is, Hurpin *et al.* specifically teaches away from the claimed invention by teaching that naked DNA works whereas the administration of a recombinant canarypox vector, such as one would use to express a p53 in a target cell, does not. Further, the canarypox data teaches away from the use of intradermal administration for viral vectors, given that intravenous administration was the only route that worked for canarypox-p53.

Therefore, Hurpin simply cannot be properly combined with any reference teaching viral delivery of expression constructs to target cells. In order to combine the references for a rejection under 35 U.S.C. §103 there must be some teaching, suggestion, or motivation to combine the references found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Here, not only is there not motivation to combine the references, but there is a teaching away of the combination. Where references taken in combination would produce a "seemingly inoperative device," such references teach away from the combination and thus cannot serve as predicates for a *prima facie* case of obviousness. *In re Sponnoble*, 405 F.2d 578, 587, 160 USPQ 237, 244 (CCPA 1969); *see also In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). This is because the Federal Circuit has noted that, as a "useful general rule," references that teach away cannot serve to create a prima facie case of obviousness. *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1131, 1132 (Fed. Cir. 1994).

The Action, nonetheless, states that Reed *et al.* provides further motivation for substituting the vector of Fang *et al.* for the plasmid vector of Hurpin by teaching that recombinant human viral vectors have advantages including high transduction efficiency and the ability to produce stable high-titer stocks. However, this misses the point made above, which is that Hurpin *et al.* teaches away from the use of viral vectors and instead suggests the use of "naked DNA." One of skill in the art would thus not be motivated to use the vectors of Reed *et al.* or Fang *et al.*, because Hurpin teaches that naked DNA in the form of a plasmid works better. That Reed may teach that recombinant human viral vectors have certain advantages for high transduction efficiency is inapposite, as what is relevant is the claimed method, not distinct prior art techniques.

The Action further alleges various other teachings of Reed *et al.* in the Action. For example, it is stated that Reed *et al.* teaches that MAGE-1 are recognized as capable of stimulating and being lysed by human CTL and that Reed *et al.* suggests the utility of adenovirus vaccines encoding tumor antigens for treating cancer in human patients. However, Reed does nothing to cure the teaching away from the use of viral vectors in Hurpin *et al.* For example, unlike the current invention, Reed *et al.* concerned the direct infection of melanoma cells. Further, the studies carried out by Reed *et al.* were done *ex vivo*. In contrast, step b) of claim 1 of the instant application comprises "(ii) intradermally administering to said subject an expression construct in a viral particle comprising a self gene under the control of a promoter operable in eukaryotic dendritic cells, wherein the dendritic cells are infected by said construct." As such, the cited references cannot be combined to arrive at the invention.

Finally, the statements in the Action itself weigh against the alleged obviousness of the claimed method. For example, at page 7 of the Action, in a rejection under 35 U.S.C. §112, first

paragraph, it is stated that "[t]he art at the time of filing also teaches the high level of unpredictability of generating therapeutic levels of gene expression using currently available expression vectors." Thus, if this statement is taken as true, it is strong evidence against the alleged obviousness of the claims.

In view of the foregoing, Applicants respectfully request removal of the rejection under 35 U.S.C. § 103.

2. ***Rejection of claims 1 and 34-37 under 35 U.S.C. §103(a) over Hurpin et al. in view of Xiang et al. in further view of Rosenthal et al.***

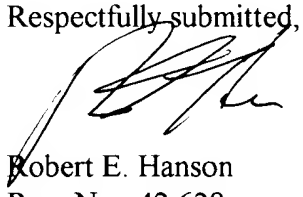
The Action rejects claims 1 and 34-37 under 35 U.S.C. §103(a) over Hurpin *et al.* in view of Xiang *et al.* ((1995) Immunity, Vol. 2, 129-135) in view of Rosenthal *et al.*, ((1994) Blood, Vol. 83(5),1289-1298). Applicants respectfully traverse.

The Action fails to meet the burden of establishing a *prima facie* case of obviousness with respect to claim 1 and, therefore, dependent claims 34-37. In particular, the Action recites various portions of Xiang *et al.* and Rosenthal *et al.* said to teach expression of cytokines, antigens and combinations thereof, but fails to establish a case of *prima facie* obviousness with respect to claim 1 for the same reasons set forth above. As described herein above in detail, Hurpin *et al.* teaches away from the delivery of an expression construct using viral particles and thus cannot be properly combined with the cited references to establish a *prima facie* case of obviousness. The currently cited references have not been alleged to add anything with respect to this shortcoming of the rejection of claim 1. Therefore, as indicated in detail herein above, the claims are not *prima facie* obvious. Removal of the rejection under 35 U.S.C. §103 is thus respectfully requested.

E. Conclusion

In light of the preceding amendments and remarks, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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APPENDIX A: VERSION OF CLAIM AMENDMENTS MARKED TO SHOW CHANGES

1. (Amended) A method for treating a human subject with a hyperproliferative disease comprising the steps of:

(i) identifying a subject with a hyperproliferative disease characterized by alteration or increased expression of a self gene product in at least some of the hyperproliferative cells in said subject [patient]; and

(ii) intradermally administering to said subject an expression construct in a viral particle comprising a self gene under the control of a promoter operable in eukaryotic dendritic cells, wherein the dendritic cells are infected by said construct,

whereby said self gene product is expressed by dendritic cells and presented to immune effector cells, thereby stimulating an anti-self gene product response.